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Synthesis, Characterization and Biological activities of 2-Amino-3-Methyl pyridine New Dithiocarbamate metal complexes

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ABSTRACT

Dithiocarbamates are a class of sulfur-based metal-chelating compounds with various applications in medicine. A new series of new transition metal [Cu(II), and Ni(II)] complexes of dithiocarbamates were synthesized from 2-Amino-3-Methyl pyridine and Carbon disulfide and further characterized. The investigation of these complexes confirmed that the stability of metal–ligands coordination through, S&S,N atoms as bidendate chelates.. It is necessary to understand the binding properties in developing new potential Protein targeting against neurological disorders.

Keywords:2-Amino-3-Methylpyridine,MetalComplexes,Dithiocarbamates,neurological disorders.

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INTRODUCTION

The field of Dithiocarbamate metal complexes are vast and fast developing on account of their spectacular applications in various fields, also owing to the varieties of structural forms of the ligands. The ever-increasing applications of transition metal complexes in different fields of sciences are the driving force for the present research[1].The Dithiocarbamates are organosulphur compounds considered to be versatile organic ligands which form complexes with many transition metals like Cu, Fe, Ni, Mn and Zn leading to the stabilization of a wide range of oxidation states.

The complexing ability of dithiocarbamates is well established and this is due to two sulphur atoms, which are capable to donate a lone pair of electrons to the central metal atom to form the stable metal complexes[2]. These are known to stabilize unusual oxidation states of metal complexes, because of the delocalization of positive charge from the metal to nitrogen. Besides, dithiocarbamates ligand and its metal complexes exhibit their striking and diversified applications in many fields like Medicine, Agriculture Industry, Polymer technology, Inorganic and Environmental trace analysis[3].

Dithiocarbamates ligands are soft bases. They had been found to act almost as uni negative bidentate ligands coordinating through sulphur atoms, and also both tetra and hexa co-ordinate complex of many transitional metal ions have been isolated[4-6]. They exhibit various applications in different fields especially in the production of petroleum derivatives, lubricants, as accelerators for vulcanization in Polymer Industry, as antioxidants and anti humidity agents. They are also having fungicidal, bactericidal, insecticidal, anticancer, and photochemical activities. Dithiocarbamates ligands itself acts as a good antibacterial and antifungal activity and are used as biocides (vapam, nabam)[6-10].

Owing to wide applicability of sulphur bearing ligands in biological and industrial field, a bulk of literature is available on the dithiocarbamates ligands and its complexes of transition and non-transition metals. A large number of transition metal complexes with various aliphatic and aromatic dithiocarbamate ligands have been reported. Though a number of dithiocarbamates have been prepared in the literature.

2-Amino3-Methyl pyridine dithiocarbamate is a dopamine agonist. Treating the signs and symptoms of Parkinson

disease. It is also used to treat restless legs syndrome (RLS). Pramipexole is used to treat symptoms of Parkinson's disease (stiffness, tremors, muscle spasms, and poor muscle control). Pramipexole is also used to treat restless legs syndrome (RLS).Only immediate-release pramipexole (Mirapex) is approved to treat either Parkinson symptoms or RLS. Extended-release pramipexole (Mirapex ER) is approved only to treat Parkinson symptoms.

Insights gained from decades of research have begun to unlock the pathophysiology of these complex diseases and have provided targets for disease-modifying therapies. In the last decade, few therapeutic agents designed to modify the underlying disease process have progressed to clinical trials and none have been brought to market. With the focus on disease modification, biomarkers promise to play an increasingly important role in clinical trials. Among the histamine receptor subtypes, H3 receptors play an important regulatory role in the CNS. Activation of H3 auto receptors can inhibit histamine synthesis and release from histaminergic neurons, while activation of H3 hetero receptors can inhibit release of other neurotransmitters such acetylcholine, noradrenaline, dopamine and 5-HT from non-histaminergic neurons. Conversely, blockade of H3 receptors with selective antagonists can increase the release of neurotransmitters involved in cognitive processes. Selective H3 receptor antagonists have been shown to improve performance in a diverse range of rodent cognition paradigms, and can also increase wakefulness. This has led to the development of H3receptor antagonists for the potential treatment of several CNS disorders including cognitive dysfunction in Alzheimer's disease (AD).

Parkinson's disease (PD) is one of the most common diseases of the central nervous system (CNS). It is frequently heralded by speech disturbances, which are one of its first symptoms. Parkinson's disease (PD) is a progressive extra pyramidal motor disorder. Pathologically, this disease is characterized by the selective dopaminergic (DAergic) neuronal degeneration in the *Substantia nigra*. Correcting the DA deficiency in PD with levodopa (Ldopa) significantly attenuates the motor symptoms; however, its effectiveness often declines, and L-dopa-related adverse effects emerge after long-term treatment. Nowadays, DA receptor agonists

are useful medication even regarded as first choice to delay the starting of L-dopa therapy. In advanced stage of PD, they are also used as adjunct therapy together with L-dopa. DA receptor agonists act by stimulation of presynaptic and postsynaptic DA receptors. Despite the usefulness, they could be causative drugs for valvulopathy and nonmotor complication such as DA dysregulation syndrome (DDS).It is necessary to understand the binding properties in developing new potential Protein targeting against neurological disorders.

The present work has been extended to know antibacterial activity, anti inflammatory activity and antifungal activity of the dithiocarbamates metal complexes.

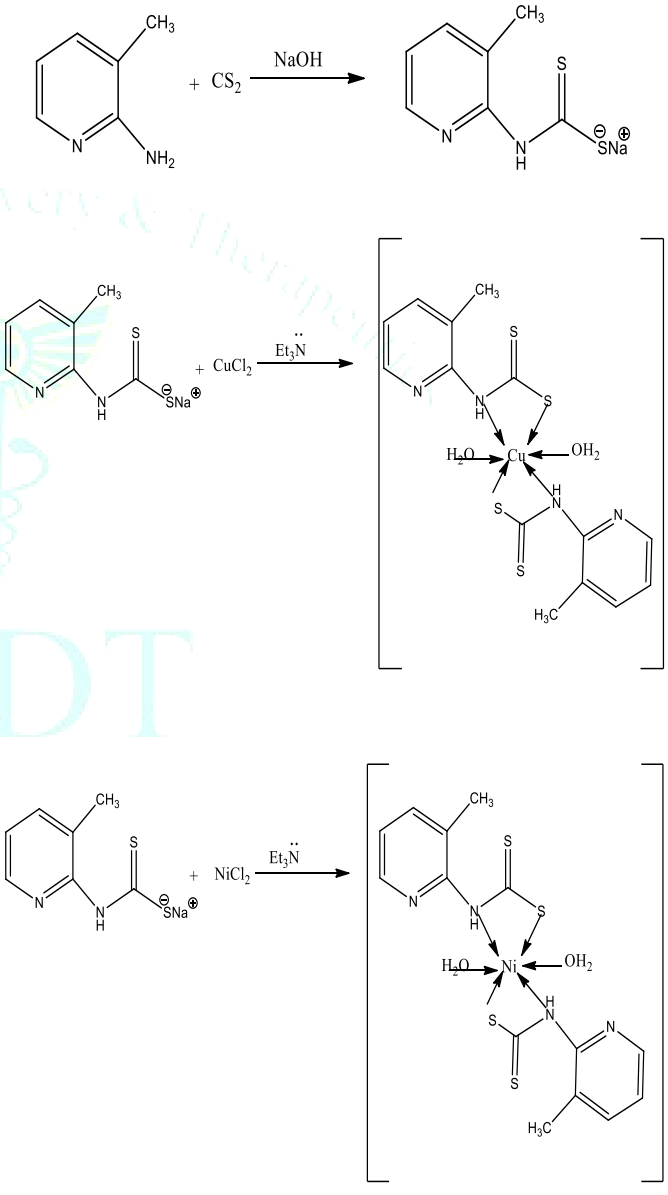
The main thrust of the study is to prepare as such new dithiocarbamates ligand from an amine having considerable amount of applications on its own with the hope that the resultant dithiocarbamates may possess much more applications and find a place in major fields of interest.

MATERIALS AND METHODS

Experimental Section

Copper chloride anhydrous was obtained from Fluka, Pramipexole and carbon disulfide were purchased from Aldrich. Other chemicals used were of analytical reagent or higher purity grade. Solvents used were of reagent grade and purified before use by the standard methods. Conductivity measurement was carried out by a Systronics Conductivity Bridge 305, using a conductivity cell of cell constant 1.0 double distilled water was used as solvent. Electronic absorption spectra on JAS.CO UV/VIS-7850 recording spectrophotometer. Infrared spectra were recorded on a JAS.Co-460 plus FT-IR spectrophotometer in the range of 4000-400 cm^{-1} in KBr pellets. Microchemical analysis of carbon, hydrogen and nitrogen for the complexes were carried out on a Herause CHNO-Rapid elemental analyzer.^{1}H NMR spectra were recorded on a Brucker DRX-500 Advance spectrometer at 500MHz in DMSO-discussing tetramethylsilane as internal reference standard. Melting points were measured on a unimelt capillary melting Point apparatus and reported uncorrected.

Synthesis of 2-Amino-3-Methyl pyridine dithiocarbamate



Preparation of Sodium salt of Dithiocarbamate ligands

0.05 mol of 2-Amino-3-Methyl pyridine was dissolved in 30 ml of absolute alcohol in a clean beaker which was placed in ice bath. To this cold solution add 5 ml of Sodium hydroxide (10N) solution, and then add Pure carbon disulphide (0.05ml) in drop wise with constant stirring. The contents

were stirred mechanically for about 30 min, sodium salt of dithiocarbamates precipitated out. It was dried over and recrystallized from ethanol.

Preparation of Cu (II) andNi (II) Complexes

Synthesis of [Cu (ADTC)$_2$)Cl$_2$]

The aqueous solution of 0.05 mol of Cupper Chloride was added with constant stirring to an aqueous solution of 0.01 mol of Sodium salt of 2-Amino-3-Methyl pyridine dithiocarbamate ligand. The reaction mixture was stirred at room temperature for 2 hours. The colored (Blue) precipitates were obtained. The precipitates were filtered and washed with water and then with methanol and dried over calcium chloride in desiccator's Yield: 78% and decomposes at 110 C.

Anal.Calcd.C16H24CuS4N4O2;ForC,38.73;H,4.88;N,11.29;Cu,12.81;O,6.45,S,25.85;
Found:C,38.78;H,4.93;N,11.32;Cu,12.94;O,6.50,S,25.90

Synthesis of [Ni (ADTC)Cl$_2$]

The aqueous solution of 0.05 mol of Nickel Chloride was added with constant stirring to an aqueous solution of 0.01 mol of Sodium salt of 2-Amino-3-Methyl pyridine dithiocarbamate in the presence of small quantity of triethylamine. The reaction mixture was stirred at room temperature for 2 hours. The colored (green) precipitates were obtained. The precipitates were filtered and washed with water and then with methanol and dried over calcium chloride in a desiccator Yield:80% and decomposes at 110^{0}C.

Anal. Calcd. C16H24NiS4N4O2 For C, 39.11; H, 4.92; N, 11.40; O, 6.51; S, 26.10; Ni, 11.95 Found: C:39,16; H:4.97; N:11.40; O, 6.56; S:26.15; Ni, 11.98

RESULTS AND DISCUSSION

Solid reflectance spectra data for the Cu and Ni of 2-Amino-3-Methyl pyridine metal complexes. The complexes [Cu(ADTC)$_2$)Cl$_2$] and [Ni(ADTC)$_2$Cl$_2$] complexes exhibit magnetic property and has an electronic spectrum which can be assigned to low spin Cu(II) and Ni(II) in an Octahedral Environment. Intra ligand electronic transition in then…C…S…S and S…C…S chronophers of the dithiocarbamate moiety. Thus the peak at 646 nm and the shoulder at 499 summarized from 1A1g_1T1g and 1A1g_1T2g transitions, respectively. The other lower peaks are probably charge-transfer in origin.

Infrared Spectrum

Two regions of the IR spectrum of the [Cu(ADTC)$_2$)Cl$_2$] and [Ni(ADTC)$_2$Cl$_2$] complex have proven valuable in arguments concerning the electronic and structural characteristics of this compound. The presence of the thiouride band between 1496-1404 cm^{-1}suggest a considerable double bond character in the C…N bond vibration of the S_2C-NR_2 group. The band present in the 967-1071cm^{-1} range is attributed to the prevailing contribution of (C…S) Vibrations in these ranges have been used defectively in differentiating between monodentate, bidentate dithiocarbamate ligands. The presence of only one strong band supports bidentate coordination of the dithio ligands, whereas a doublet is expected in the case of monodentate coordination. (C…S) and (C..N) Stretching frequencies fall in the 1047 cm^{-1} (1001 cm^{-1} to 1490 cm^{-1} respectively for the free ligand). The methyl group in the complex, as medium strong bands in the 2924 cm^{-1} range can be related to the asymmetric CH_3 stretching vibration.

H^1-NMR Spectra

The NMR spectrum of the [Cu(ADTC)$_2$)Cl$_2$] and [Ni(ADTC)$_2$Cl$_2$] complexes showed at7.70 ppm, which may be assigned to the hydroxyl protons. The peak at 7.9-9.76 attributed to NH protons of thiouraide nitrogens in both complexes. In other signals is also appeared in the region 0.90,1.5,3.8 ppm.N

Antimicrobial Activity

Antimicrobial test was performed on four bacterias (*Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa,*) and two fungi (*Candida albicans and Candida tropicalis*). The media used were prepared by dissolving separately 2g of nutrient broth powder and 38g of the Mueller-Hinton agar powder in250 ml and 1 L of deionized water, respectively. Two media were sterilized in an autoclave at 121^{0}C for 15 minutes and then stored overnight in a refrigerator after cooling. Cultures of the microorganisms were prepared in sterile nutrient broth and incubated for 24 hours at 37^{0}C for the bacteria and 27^{0}Cfor the fungi.0.1 ml of each of the overnight cultures in sterile test tubes with caps were made up to 10 ml with 9.9 ml of sterile deionized water

Growth inhibition zone in millimeter(mm)						
BACTERIA					**FUNGUS**	
	Gram +Ve		**Gram -Ve**			
	S.aur	**B.subt**	**E.coli**	**P.aerug**	**C.alb**	**C.trop**
Cu(ADTC)	14	14	15	14	14	15
Ni(ADTC)	12	14	14	13	16	15
FLU			------	-----	15	15
DMSO	12	14	15	16	-----	----

To give 1:100 or 10-2 dilution of the microorganisms. The technique used for the study was agar-well diffusion. Solutions of concentration 10 mg/ml of the compounds were made in dimethyl sulphoxide (DMSO). DMSO was also used as the negative control. Positive controls for bacteria and fungi were discs of commercial antibiotics manufactured by Abtek Biological Limited and Fluconazole dissolved in DMSO. The discs were carefully placed on the inoculated media with the aid of sterile forceps. Plates inoculated with bacteria were incubated at 37^{0}C for 24 hours, and those inoculated with fungi were incubated at 27^{0}C for 72 hours. Afterwards, the zones of inhibition of microbial growth that appeared around the wells of the compounds were examined and the diameters measured and recorded in millimeters (mm). Antimicrobial activity of the Cu(II) and Ni(II) complexes was evaluated *in vitro* against Gram positive bacteria-*Staphylococcus aureus*and *Bacillus subtilis*, Gram negative bacteria-*Escherichia coli*, *Pseudomonas aeruginosa* and fungi, *Candida albicans*, *Candida tropicalis.* The results for the complexes and commercial antibiotics used as positive controls are listed in (Table 1).

CONCLUSION

Cu (II) and Ni(II) complexes of 2-Amino-3-Methyl pyridine dithiocarbamate ligand with have been synthesized and characterized. The ligand moiety exhibits a bidentate coordination mode in the Cu (II) and Ni (II) complexes. Solid reflectance spectra and magnetic data indicate that the complexes are Paramagnetic and Octahedral. The complexes show selective activity towards some of the test microorganisms. In this Study, we have docking studies of H3 receptor model with dithiocarbamate ligand and metal complexes having more favorable rank score, docking score and hydrogen bonding energy and the binding pocket of the H3 receptor. Activation of H3 hetero receptors can inhibit release of other neurotransmitters such acetylcholine, noradrenaline, dopamine, conversely blockade of H3 receptors with our synthesized selective antagonists can increase the release of neurotransmitters involved in cognitive processes. The biological studies of dithiocarbamate ligand and metal complexes with H3 receptor and detailed analyses of metal inhibitors, H3 receptor interactions were done and the residues in binding responsible for binding to the inhibitors of metal substrates with high binding affinity were identified. Hence we conclude that these dithiocarbamate ligands and metal complexes could be a potential anti Neurological disorders lead molecules for modulating the expression of H3 receptor in Parkinson's disease (PD) and Alzheimer's disease (AD) supports for experimental testing.

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